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ORIGINAL ARTICLE

Treatment of ventilator-associated pneumonia (VAP) caused by *Acinetobacter*: results of prospective and multicenter ID-IRI study

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Abstract

Ventilator-associated pneumonia (VAP) due to *Acinetobacter* spp. is one of the most common infections in the intensive care unit. Hence, we performed this prospective-observational multicenter study, and described the course and outcome of the disease. This study was performed in 24 centers between January 06, 2014, and December 02, 2016. The patients were evaluated at time of pneumonia diagnosis, when culture results were available, and at 72 h, at the 7th day, and finally at the 28th day of follow-up. Patients with coexistent infections were excluded and only those with a first VAP episode were enrolled. Logistic regression analysis was performed. A total of 177 patients were included; empiric antimicrobial therapy was appropriate (when the patient received at least one antibiotic that the infecting strain was ultimately shown to be susceptible) in only 69 (39%) patients. During the 28-day period, antibiotics were modified for side effects in 27 (15.2%) patients and renal dose adjustment was made in 38 (21.5%). Ultimately, 89 (50.3%) patients died. Predictors of mortality were creatinine level (OR, 1.84 (95% CI 1.279–2.657); p = 0.001), fever (OR, 0.663 (95% CI 0.454–0.967); p = 0.033), malignancy (OR, 7.095 (95% CI 2.142–23.500); p = 0.001), congestive heart failure (OR, 2.341 (95% CI 1.046–5.239); p = 0.038), appropriate empiric antimicrobial treatment (OR, 0.445 (95% CI 0.216–0.914); p = 0.027), and surgery in the last month (OR, 0.137 (95% CI 0.037–0.499); p = 0.003). Appropriate empiric antimicrobial treatment in VAP due to *Acinetobacter* spp. was associated with survival while renal injury and comorbid conditions increased mortality. Hence, early diagnosis and appropriate antibiotic therapy remain crucial to improve outcomes.

Keywords Ventilator-associated pneumonia · VAP · Pneumonia · *Acinetobacter* · Mortality · Treatment

Introduction

Ventilator-associated pneumonia (VAP) is one of the most common infections in the intensive care unit (ICU) [1, 2]. The disease represents a diagnostic and management dilemma to clinicians [3] and is associated with significant mortality in patients [4]. *Acinetobacter* strains, once considered a low-category pathogen, have become an important etiology of VAP in ICUs worldwide [5, 6]. Patients with serious comorbidities that need mechanical ventilation can become infected with antibiotic-resistant *Acinetobacter* spp., representing a therapeutic challenge [7, 8]. There is a paucity of information on VAP due to *Acinetobacter* spp. Thus, we performed this prospective-observational multicenter study, and described the course, prognostic factors, and outcomes of VAP due to *Acinetobacter* spp.

Methods

An observational, prospective study was performed in 24 medical centers between January 06, 2014, and December 02, 2016. Dr. Lutfi Kirdar Education and Training Hospital's Review Board in Istanbul approved the study (02/01/2014-VIP 2014/1) and this approval was confirmed by the Turkish

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Ministry of Health, Drugs and Pharmaceutics Agency for all participating centers. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Appropriate empiric antimicrobial treatment was defined if the patient received at least one antibiotic that the infecting strain was ultimately shown to be susceptible. The laboratories of the participant centers used Vitek-2 (n = 20), BD Phoenix M50 (n = 2), broth microdilution (n = 1), and Microscan 96 (n = 1) for antibiotic susceptibility testing in the participating centers in accordance with EUCAST guidelines during the study period [9–11]. In addition, E-test was used as a complementary method to Vitek-2 in three centers. Multidrug resistance (MDR), extensively drug resistance (XDR), and pan-drug resistance (PDR) were classified according to definitions elsewhere [12].

Data collection and procedures

The same questionnaire was used throughout all participant centers and the data input was made available to centers through the internet. The patients enrolled in the study were regularly evaluated by the consulting infectious disease physician at the time of pneumonia suspicion/diagnosis, when antibiotic susceptibility testing (AST) results were available, at 72 h, at the 7th day, and finally at the 28th day of follow-up. All antibiotics were prescribed by an infectious disease physician. The decision to start or modify antimicrobial chemotherapy was made by infectious disease clinicians. There was no policy for clinicians to choose antimicrobials in the study protocol.

Inclusion criteria

1. Age ≥ 18 years
2. Patients mechanically ventilated (> 48 h)
3. Pulmonary infection due to *Acinetobacter* spp. as the first episode
4. Presence of systemic, radiological, clinical/pulmonary, and microbiological findings indicating VAP [13]
5. Empirical antibiotic therapy should have been started
6. Written consent should be obtained either from the patient or from her/his close relatives

Exclusion criteria

1. Pregnancy
2. The presence of concordant/coexistent infection other than VAP
3. Presence of an infection detected preceding VAP or if the patient was still given antibiotics at the time of VAP diagnosis
4. The recovery of other bacteria along with the infecting *Acinetobacter* spp. either in blood or in bronchial samples
5. If qualitative cultures of respiratory specimens were done solely

Missing data Cases with missing and/or outliers were asked to be corrected by the researcher of the center. Variables with more than 30% missing value between all candidate predictors were dropped according to the White et al.'s proposed rule of thumb. In this rule, the number of imputations used was matched to the proportion of missing data [14]. We applied the "the missing completely at random" (MCAR) procedure for the missing data to define missing mechanisms of variables for either dropping or imputing before performing multiple imputation for the cases and columns < 30% [15]. The hypothesis of MCAR was rejected at the 0.05 level by the normality test; therefore, dropping the missing observations would produce biased estimates. We imputed the missing observations 20 times. We also generated a complete dataset by aggregating the set of twenty imputations to the medians [16].

Statistical analysis Univariate and logistic regression analyses were done to identify predictors for mortality. The data was obtained on the day that the antibiotics were started. Parametric and non-parametric data were differentiated from quantitative data (continuous variables). In univariate analysis, the differences between the groups of mortality were examined using Student's t test for parametric and Mann–Whitney U test for non-parametric tests. Consultation within the study working group was used when collinearity was suspected to select which variable to retain on the basis of perceived clinical value, reliability of measurement, and availability. Backward Wald method was used for binary logistic regression analysis. $p < 0.05$ was accepted as significant for further analyses. Using consultation within the study working group, the APACHE score was excluded from the regression analysis as the potential source of collinearity.

The parameters we included in univariate analyses at the start of antibiotics were the following: patient characteristics, underlying comorbid conditions and invasive procedures, clinical signs and findings, radiological data, antibiotic susceptibility data and categories (MDR, XDR), and the antibiotics used.

Results

A total of 245 patients were enrolled in the study. We excluded 61 cases with missing follow-up data and 7 more patients that did not meet microbiological requirements (missing data > 30%). Hence, we included 177 cases. The median antibiotic use period of the patients was (IQR) 13 (9–19.25) days. A

Table 1 Risk factors for acquisition of VAP due to *Acinetobacter* spp.

Variable	*N* = 177
Underlying comorbidities	*n* (%)
Hypertension	70 (39.5)
COPD	50 (28.2)
Cerebrovascular disease	43 (24.3)
Diabetes mellitus	41 (23.2)
Congestive heart failure	40 (22.6)
Acute renal failure	34 (19.2)
Coronary artery disease	34 (19.2)
Surgery	28 (15.8)
Malignancy	27 (15.3)
Trauma	21 (11.9)
Chronic renal failure	11 (6.2)
Immunosupressive treatment	10 (5.6)
Chronic liver disease	4 (2.3)
Splenectomy	3 (1.7)
Neutropenia	2 (1.1)
Burn	1 (0.6)
HIV infection	1 (0.6)
Connective tissue disorder	1 (0.6)
Invasive procedures	*n* (%)
CVC	146 (82.5)
• Internal jugular	75 (51.4)
• Subclavian	54 (37.0)
• Femoral	17 (11.6)
Urinary catheter	175 (98.9)
Nasogastric tube	131 (74.0)
Tracheostomy	43 (24.3)
Drainage catheter	21 (11.9)

VAP, ventilator-associated pneumonia; *COPD*, chronic obstructive pulmonary disease; *HIV*, human immunodeficiency virus; *CVC*, central venous catheter

total of 8 missing values (4.52%) of creatinine met the MCAR assumptions.

I. Initial assessment

(a) Patient characteristics: The median (IQR) age of the patients was 68 (52.5–79) years; 120 patients (67.8%) were males. Underlying comorbid conditions and invasive procedures of the patients are presented in Table 1.
(b) Start of antimicrobial therapy: The median (IQR) time period between mechanical ventilation and start of antibiotics was 6 (2–12) days.
(c) Colistin use: Colistimethate sodium (CMS) was the available formulation in the market during the study period and was used when necessary. The details of CMS use at the start of therapy are presented in Fig. 1. All patients were treated with standard antibiotic dosages (https://www.sanfordguide.com/).

II. The assessment of initial culture results

Acinetobacter spp. were recovered in blood cultures in 23 (13.0%) patients, in ETA of 155 (87.6%) cases, and BAL in 26 (14.7%). Multiple cultures were positive for *Acinetobacter* spp. in 37 (21%) patients. The AST results of *Acinetobacter* spp. are presented in Table 2. In total, 136 MDR (76.8%), 38 XDR (21.5%), 1 PDR, and 2 susceptible strains were recovered. When the patients were evaluated according to AST data, 69 (39%) initially received appropriate empirical antimicrobial treatment.

III. Overall assessment (28th day of appropriate antimicrobial treatment)

(a) Outcome: On the 28th day of follow-up assessment, 89 (50.3%) patients had died. The median time to death (IQR) was 10 (7–16) days.
(b) Drug modification: During the 28-day period, antibiotics were modified in 14 patients on the 3rd day of assessment and it was modified on the 7th day in 16 patients. In 3 cases, modification was made in both timings reaching

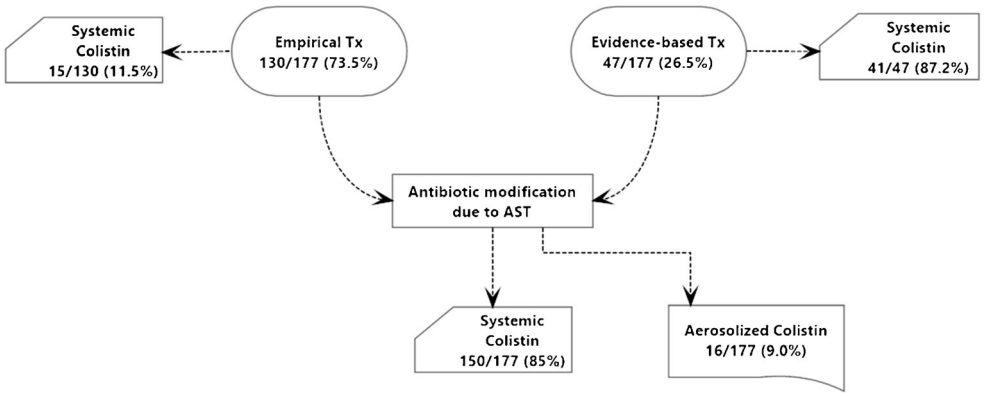

Fig. 1 Colistin use at the start of therapy

Table 2 Antimicrobial susceptibility data of 177 *Acinetobacter* spp. isolates

Antibiotics (*n*)	Resistant (%)
Colistin (175)	2 (1.1)
Tigecycline (104)	40 (38.5)
Amikacin (174)	143 (82.2)
Gentamicin (173)	150 (86.7)
Imipenem (175)	171 (97.7)
Meropenem (175)	172 (92.3)
Piperacillin–tazobactam (160)	159 (99.4)
Cefoperazone–sulbactam (141)	130 (92.2)
Ampicillin–sulbactam (160)	156 (97.5)
Trimethoprim sulfamethoxazole (173)	147 (85.0)
Ciprofloxacin (177)	172 (97.2)

a sum of 27 on the whole. Hence, crude mortality was 48% (n = 72) in patients without modification and it was 63% (n = 17) with modification.

(c) Antibiotic dosing: During the 28-day period, a CMS loading dose (300 mg) was given in 21 of 150 (14%). Renal dose adjustment was made in 23 patients on the 3rd day of assessment while redosing was made on the 7th day in 15 patients. In 5 patients, dose adjustment was made in both timings reaching a total of 38. Hence, crude mortality was 45.8% (n = 66) in patients without adjustment and it was 70% (n = 23) with modification.

(d) Prognostic assessment: Table 3 shows the parameters associated with mortality in univariate analyses and final logistic regression model. Consequently, appropriate empiric antimicrobial treatment (OR, 0.445 (95% CI 0.216–0.914); p = 0.027), surgical operations performed in the last month (OR, 0.137 (95% CI 0.037–0.499); p = 0.003), fever (OR, 0.663 (95% CI: 0.454–0.967); p = 0.033), creatinine levels (OR, 1.84 (95% CI 1.279–2.657); p = 0.001), malignancy (OR, 7.095 (95% CI 2.142–23.500); p = 0.001), and congestive heart failure (OR, 2.341 (95% CI 1.046–5.239); p = 0.038) at the start of

Table 3 Outcome analysis of 177 patients with VAP due to *Acinetobacter* spp.

Univariate analyses, significant parameters				
	Death	Survival	Total	*p* value
Diabetes mellitus	27 (30.3%)	14 (15.9%)	41 (23.2%)	0.032*
Malignant diseases	19 (21.3%)	8 (9.1%)	27 (15.3%)	0.035*
Congestive heart failure	26 (29.2%)	14 (15.9%)	40 (22.6%)	0.047*
Trauma	3 (3.4%)	18 (20.5%)	21 (11.9%)	< 0.001*
Ciprofloxacin-resistant *Acinetobacter*	0 (0.0%)	5 (5.7%)	5 (2.8%)	0.029*
Acute renal failure	22 (24.7%)	12 (13.6%)	34(19.2%)	0.085*
Hypertension	41 (46.1%)	29 (33.0%)	70 (39.5%)	0.091*
Surgical operation in the last month	6 (6.7%)	22 (25.0%)	28 (15.8%)	0.001*
Judicious treatment (empirical)	29 (32.6%)	40 (45.5%)	69 (39.0%)	0.091*
APACHE-II	24 (6–66)	18 (1–45)	21 (1–66)	< 0.001**
Median (min–max)				
Creatinine value	1.10 (0.10–5.60)	0.70 (0.18–5.60)	0.80 (0.10–5.60)	< 0.001**
Median (min–max)				
Fever	37.8 (35.7–40.2)	38.3 (36.0–40.5)	38.0 (35.7–40.5)	0.004**
Median (min–max)				
Logistic regression analysis				
			95% C.I. for EXP(B)	
	Sig.	OR	Lower	Upper
Creatinine	0.001	1.843	1.279	2.657
Fever	0.033	0.663	0.454	0.967
Malignant diseases	0.001	7.095	2.142	23.500
Congestive heart failure	0.038	2.341	1.046	5.239
Judicious treatment (empirical)	0.027	0.445	0.216	0.914
Surgical operation in the last month	0.003	0.137	0.037	0.499
Constant	0.040	3,071,378.735		

VAP, ventilator-associated pneumonia

*Fisher's exact test, **Mann-Whitney *U*

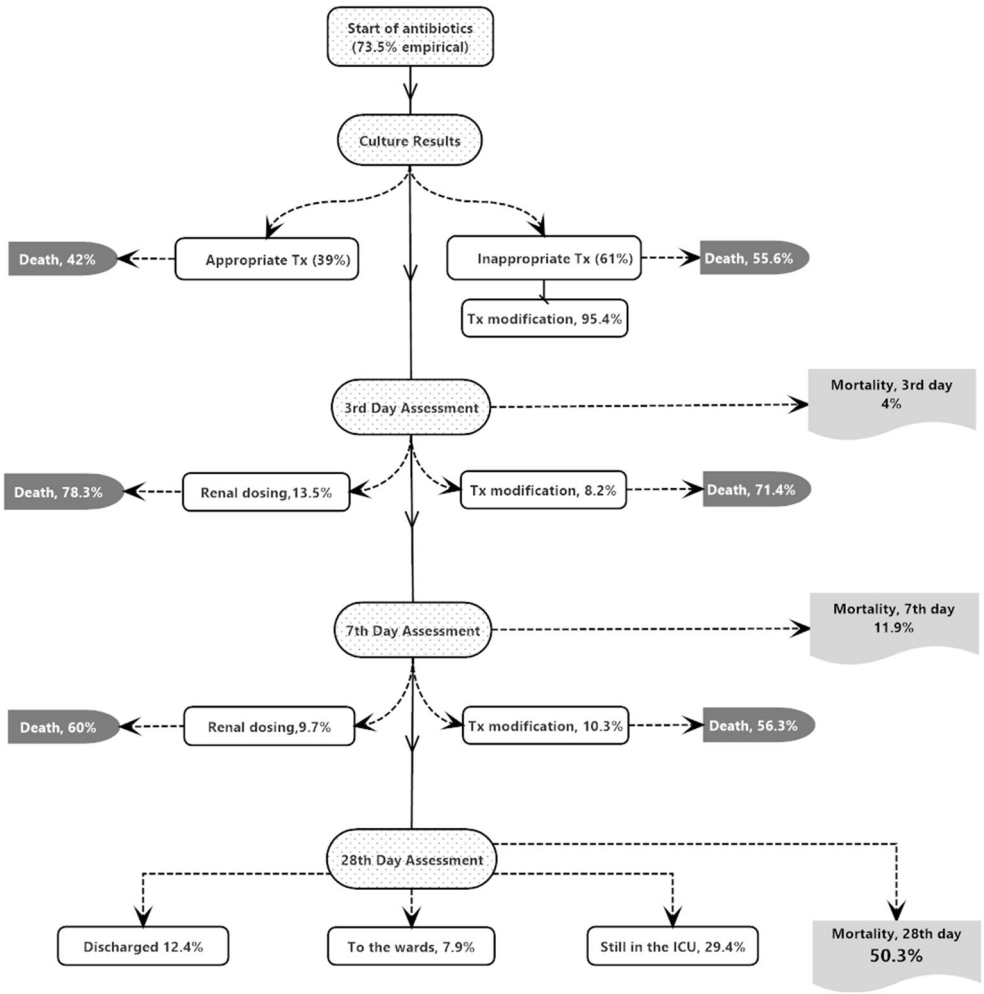

Fig. 2 Therapeutic courses in VAP due to *Acinetobacter* spp.

antibiotics were significantly associated with mortality. The course of anti-infective treatment is presented in Fig. 2.

Discussion

Infections due to *Acinetobacter* spp., particularly VAP in the ICUs, are mostly seen in critically ill or debilitated patients [17]. After 1 month of follow-up, half of the cases with VAP due to *Acinetobacter* spp. died in this study. The magnitude of the problem indicates the need for optimizing the diagnosis and therapy of these infections. We report that therapeutic options were quite limited and involved serious toxicities for patients with VAP due to *Acinetobacter* spp. In addition, the use of appropriate empirical antimicrobial therapy contributed to survival of patients along with recent surgery and fever. We hypothesize that a high fever favors a robust immunity, and surgical operation in the last month as an acute disorder without permanent chronic conditions. In contrast, renal insufficiency indicated by high creatinine levels considering the nephrotoxic potential of CMS, the backbone of therapy, or comorbid conditions like congestive heart failure and malignancy significantly contributed to a poor prognosis.

Although carbapenem resistance differs throughout the world being less common in high-income countries [8], more than 95% of *Acinetobacter* isolates were resistant to carbapenems in our study. Interestingly, although inappropriate antibiotic treatment contributed to mortality, we could not show a difference between XDR and MDR strains for survival. CMS seemed to be the major option in the management of the disease followed by tigecycline as a potential alternative. When carbapenem resistance exceeds 20% in a given community, then empiric CMS combination with a carbapenem (other than ertapenem), tigecycline, or sulbactam is advocated [18]. However, tigecycline has limitations due to low plasma levels limiting its use in bacteremias [19]. Accordingly, the use of tigecycline in VAP was shown to be hampered in a phase III randomized controlled trial disclosing higher mortality in the tigecycline arm [20]. Under these peculiar circumstances, what should the treating clinicians do when our data are considered? Should CMS-based regimens be given to all VAP patients as empirical treatment? This controversy is also

reflected in our study since the physicians prescribed CMS-based regimens empirically in 11.5% of the cases while CMS was prescribed in 87.2% of the patients following AST results. Although we have disclosed that appropriate treatment contributed to survival in this study, empirical CMS use will surely result in the rapid loss of the unique option. No concrete answer seemingly exists for this dilemma even in the guidelines [21]. One potential resolution may be to use rapid diagnostic tests (RDT). Cultures were taken after the start of antibiotics in 9% of our cases and it took a median of 2 days to yield AST data. These obvious delays indicate the necessity of RDTs in routine medical practice like multiplex real-time PCR or MALDI-TOF MS [18]. Considering the limitations and since most RDTs have not been validated for respiratory secretions, they should be better used together with conventional culture systems. Furthermore, antibiotic stewardship can improve survival [18, 22].

The treatment of VAP due to *Acinetobacter* spp. is a real thorny road. When the initial antibiotic therapies were evaluated according to subsequent AST data, three-fifths of the patients did not receive appropriate empiric antimicrobial treatment. After the modification of therapy after the availability of AST results, problems related to drug side effects and clinical worsening arose. In fact, patients were prone to two types of drug modification: one due to AST results, and the second due to drug side effects. Hence, VAP prevention should become a core measure and VAP prevention bundles should be implemented [23]. Unfortunately, one-third of centers from low–middle-income countries do not have these bundles in use [24].

The strengths of our study were that we excluded polymicrobial VAP and patients with coexistent infections to limit the confounders. This is also one of the largest prospective multicenter studies evaluating VAP due to *Acinetobacter*. Additionally, we only included the first VAP episode. Despite the strengths, we had limitations. First, we did not have the minimum inhibitor concentration values of all infecting *Acinetobacter* strains. Second, there could be propensity bias as treatment of patients was not randomized. Third, since the study had an observational design, it was not possible to reach a sufficient number of cases in order to analyze each independent factor that could affect the course of *Acinetobacter*-induced VAP. Appropriate empiric antimicrobial treatment, immunocompetency, and comorbid conditions affected the outcome. Surveillance of antimicrobial resistance, antibiotic stewardship, VAP prevention, diagnostic improvement, and close patient follow-up appear to have paramount importance in managing CAP patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Dr. Lutfi Kirdar Education and Training Hospital's Review Board in Istanbul approved the study (02/01/2014-VIP 2014/1) and this approval was confirmed the Turkish Ministry of Health, Drugs and Pharmaceutics Agency for all participating centers. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Informed consent Yes, informed consent is obtained.

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